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Effect of Famotidine 20 and 40 mg Dosing Regimens on the Bioavailability of Atazanavir with Ritonavir in Combination with Tenofovir in Healthy Subjects

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BACKGROUND

- Atazanavir (ATV) is a once-daily (QD) protease inhibitor (PI) extensively studied in treatment naive and experienced patients
- The inhibitory effect of low-dose ritonavir (RTV) on the metabolism of ATV is used clinically to boost exposures of ATV in the management of HIV-infected patients
- The solubility of ATV decreases with increasing pH and ATV exposures substantially decrease at intra-gastric pH > 4[1]
- Co-administration of the H_2 receptor antagonist famotidine (FAM) 40 mg twice daily (BID) with ATV 400 mg QD decreased ATV AUC and Cmin by approximately 40% each relative to ATV alone, however temporally separating administration by 2 hours mitigated the reduction in ATV exposures. Co-administration of ATV/RTV 300/100 mg QD with FAM 40 mg BID modestly reduced ATV AUC and Cmin by 18% and 28% respectively, relative to ATV/RTV 300/100 mg without FAM[2]
- Current recommendations for dosing ATV with FAM are 400 mg ATV temporally separated from FAM or ATV/RTV 300/100 mg and FAM without temporal separation in treatment-naive subjects. In treatment-experienced patients, ATV/RTV 300/100 mg at least 2 hours before and 10 hours after FAM is recommended[3]
- Tenofovir, a nucleoside reverse transcriptase inhibitor (NRTI), is commonly used as a component of the backbone regimen in the treatment of HIV-infected patients; therefore many patients may be treated with a combination of ATV/RTV and TDF (tenofovir disoproxil fumarate, a prodrug of tenofovir)
- Tenofovir decreased ATV AUC and Cmin by approximately 25% and 23% respectively, when TDF 300 mg was co-administered with ATV/RTV 300/100 mg relative to ATV/RTV without TDF[4] In a previous study, AI424-113, temporal separation of TDF 300 mg and ATV/RTV 300/100 mg by 12 hours did not substantially mitigate the reduction in ATV exposures and tenofovir Cmax and AUC were increased by approximately 34% and 37%, respectively.[5] The current clinical dosing recommendation for ATV/RTV and TDF is the simultaneous administration of ATV/RTV 300/100 mg with 300 mg TDF all as a single daily dose with food.[3] This regimen has been proven effective, despite the changes in exposures[6]
- In anticipation of an additive interaction upon simultaneous administration of ATV/RTV/TDF and FAM that may lead to a further reduction in ATV exposure, different dosing regimens of FAM, including lower doses, with ATV/RTV/TDF were explored

OBJECTIVES

Primary:

- To assess the pharmacokinetics (PK) of ATV, and identify one or more dosing regimens of ATV/RTV/TDF when dosed with FAM that would result in ATV exposures similar to those when ATV/RTV/TDF 300/100/300 was dosed without FAM

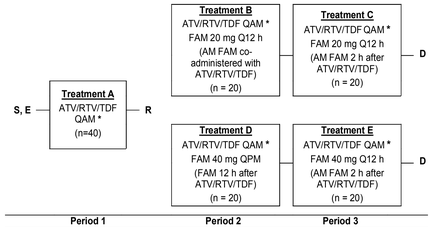
Secondary:

- To assess the PK of RTV and tenofovir when co-administered with ATV in the presence and absence of FAM
- To assess the safety and tolerability of ATV/RTV/TDF in the presence and absence of FAM

METHODS

- Randomized, open-label, multiple dose study in 40 healthy, HIV-negative adult subjects as presented in **Figure 1**

Figure 1. Study Design



S = screening; E = enrollment; R = randomization; D = discharge
QAM: every morning. QPM: every evening

*Each dose of ATV/RTV/TDF was administered as 300/100/300 mg QAM within 5 minutes of completing a light meal.

METHODS

Pharmacokinetics

- Blood samples collected up to 24 hours post-dose for ATV/RTV and tenofovir on Days 10, 17 and 24; sparse blood samples collected up to 12 hours post-dose for FAM on Days 17 and 24
- Using noncompartmental analysis, the following PK parameters were determined:
  - Cmax, Tmax, AUC(TAU) and Cmin (concentration 24 hours post-dose) for ATV, RTV and tenofovir
- Plasma samples assayed via LC-MS/MS with standard curves ranging from:
  - ATV: 10.0 - 10,000 ng/mL
  - RTV: 5.0 - 5,000 ng/mL
  - Tenofovir: 1.0 - 500 ng/mL
  - FAM: 2.0 - 300 ng/mL
  - Quality control deviations from nominal concentrations were within ±5.7% for all analytes

Statistics

- To assess the effect of FAM on the PK of ATV, RTV and tenofovir, general linear model analyses were performed on log Cmax, log AUC(TAU) and log Cmin
- Estimates for ratios of geometric means for ATV, RTV and tenofovir were obtained from exponentiation of point estimates and 90% confidence intervals (CIs) for differences on the log scales
- Summary statistics were provided for all PK parameters for ATV, RTV and tenofovir

RESULTS

Table 1. Subject Demographics and Physical Measurements

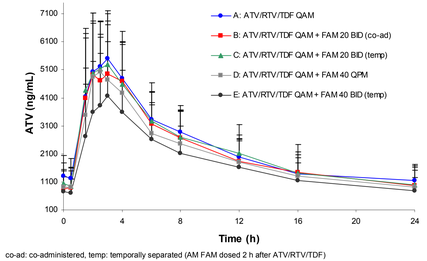
	Sequence ABC (n = 19)	Sequence ADE (n = 20)	Total (n=40)
Age (years) - Median (Range)	35 (22-48)	35 (24-46)	34 (22-48)
Sex - Male / Female	16/3	19/1	36/4
Race - n (%) Caucasian Black Asian	14 (74) 3 (16) 2 (11)	5 (25) 14 (70) 1 (5)	19 (48) 18 (45) 3 (8)
BMI (kg/m^2) - Mean (SD) Range	25.2 (3.5) 18.2 - 31.1	27.1 (2.1) 24.0 - 30.5	26.1 (3.0) 18.2 - 31.1
Height (cm) - Mean (SD) Range	172.8 (9.0) 157.0 - 191.0	176.4 (6.0) 168.1 - 189.0	174.6 (7.6) 157.0 - 191.0
Weight (kg) - Mean (SD) Range	75.4 (12.9) 60.4 - 108.5	84.6 (8.9) 70.1 - 108.8	79.7 (11.9) 60.4 - 108.8

Forty (40) subjects were enrolled and received at least a single dose of study drug. Thirty-nine (39) subjects were randomized to one of two sequences. One subject discontinued prior to randomization. Thirty six (36) subjects, 18 per sequence, completed the study. Three (3) subjects withdrew consent.

Pharmacokinetics:

Atazanavir

Figure 2. Mean (S.D.) Plasma Concentration-Time Profiles for ATV



co-ad: co-administered, temp: temporally separated (AM FAM dosed 2 h after ATV/RTV/TDF)

RESULTS

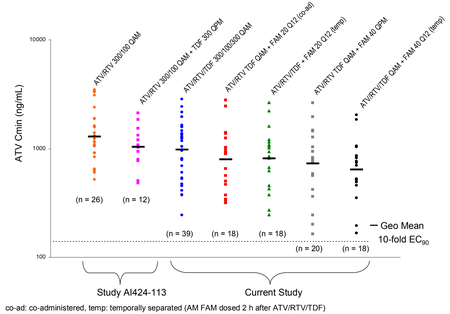
Table 2. Summary of Statistical Analyses of ATV PK Parameters

Pharmacokinetic Parameter	Geometric Means (CV%) B: ATV/RTV/TDF QAM + FAM 20 BID co-ad	A: ATV/RTV/TDF QAM	Ratios of Adjusted Geometric Means Point Estimate (90% CI)
Cmax (ng/mL)	5395 (35)	5848 (31)	0.910 (0.836, 0.991)*
AUC(TAU) (ng•hr/mL)	49144 (45)	53332 (32)	0.898 (0.820, 0.983)*
Cmin (ng/mL)	791 (71)	980 (53)	0.806 (0.689, 0.942)
	C: ATV/RTV/TDF QAM + FAM 20 BID temp	A: ATV/RTV/TDF QAM	
Cmax (ng/mL)	5651 (31)	5848 (31)	0.955 (0.861, 1.060)*
AUC(TAU) (ng•hr/mL)	52129 (37)	53332 (32)	0.955 (0.882, 1.033)*
Cmin (ng/mL)	807 (66)	980 (53)	0.823 (0.694, 0.975)
	D: ATV/RTV/TDF QAM + FAM 40 QPM	A: ATV/RTV/TDF QAM	
Cmax (ng/mL)	5104 (34)	5848 (31)	0.889 (0.814, 0.971)*
AUC(TAU) (ng•hr/mL)	44679 (43)	53332 (32)	0.876 (0.797, 0.962)
Cmin (ng/mL)	724 (68)	980 (53)	0.767 (0.634, 0.928)
	E: ATV/RTV/TDF QAM + FAM 40 BID temp	A: ATV/RTV/TDF QAM	
Cmax (ng/mL)	4087 (45)	5848 (31)	0.741 (0.657, 0.835)
AUC(TAU) (ng•hr/mL)	38039 (48)	53332 (32)	0.785 (0.703, 0.876)
Cmin (ng/mL)	641 (64)	980 (53)	0.721 (0.628, 0.827)

Subjects/Treatment: A: 39, B: 18, C: 18, D: 20, E: 18
Median Tmax ranged from 2.0 - 2.75 hours
co-ad: co-administered, temp: temporally separated (AM FAM dosed 2 h after ATV/RTV/TDF)
* Met the criteria for no-effect: 90% CI within 0.80 - 1.25

- ATV exposures in the control treatment (ATV/RTV/TDF QAM) were comparable to historical data[5]
- The data suggest a dose dependent effect of FAM on ATV exposures. ATV exposures were reduced with FAM 40 mg BID as compared to FAM 20 mg BID (co-administered or temporally separated)
- The administration of FAM 20 mg BID (either temporally separated or co-administered with ATV/RTV/TDF) did not affect ATV AUC(TAU) or Cmax and estimated reductions in ATV Cmin of <20% were observed
- FAM 40 mg once daily 12 hours after ATV/RTV/TDF minimally reduced ATV AUC(TAU) and Cmax (approximately 12% or less) relative to ATV/RTV/TDF without FAM. A reduction in ATV Cmin of approximately 23% was observed
- FAM 40 mg BID temporally separated from ATV/RTV/TDF resulted in 21% and 26% reductions in ATV AUC(TAU) and Cmax respectively. A 28% reduction in ATV Cmin was observed

Figure 3. Scatterplot of Individual ATV Cmin Values vs Treatment

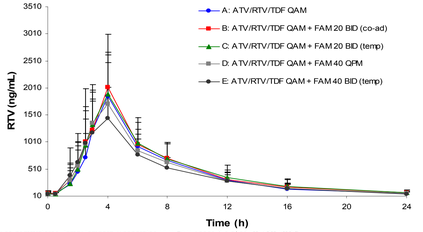


co-ad: co-administered, temp: temporally separated (AM FAM dosed 2 h after ATV/RTV/TDF)

- As demonstrated in **Figure 3**, the administration of ATV/RTV 300/100 mg with TDF 300 mg (temporally separated by 12 hours) in a previous study, AI424-113, yielded an approximate 20% reduction in ATV Cmin relative to ATV/RTV without TDF[4]
- The geometric mean ATV Cmin (980 ng/mL) after the simultaneous administration of ATV/RTV 300/100 mg with TDF 300 mg in the current study was comparable to that observed in study AI424-113 (1031 ng/mL), even though TDF was administered 12 hours after ATV/RTV
- No individual Cmin value from the healthy subjects in any of the treatment groups in the current study fell below the 10-fold protein binding adjusted EC_{90} for wild-type HIV (140 ng/mL). Note the data were collected in healthy subjects; ATV exposures would be expected to be somewhat lower in HIV-infected subjects, however Cmin values would still be expected to be well above the median wild-type EC_{90} (14 ng/mL)
- There appears to be a trend toward lower ATV Cmin values as FAM dose is increased from 20 mg BID to 40 mg BID

Ritonavir

Figure 4. Mean (S.D.) Plasma Concentration - Time Profiles for RTV

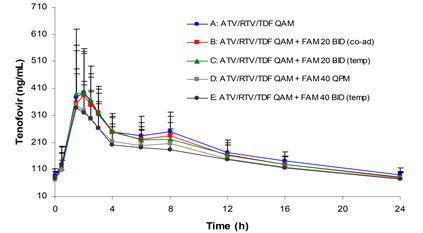


co-ad: co-administered, temp: temporally separated (AM FAM dosed 2 h after ATV/RTV/TDF)

- As noted in **Figure 4**, RTV exposures are largely unaffected by FAM; a finding that is consistent with previous results[2]

Tenofovir

Figure 5. Mean (S.D.) Plasma Concentration - Time Profiles for Tenofovir



co-ad: co-administered, temp: temporally separated (AM FAM dosed 2 h after ATV/RTV/TDF)

Table 3. Summary of Statistical Analyses of Tenofovir PK Parameters

Pharmacokinetic Parameter	Geometric Means (CV%) B: ATV/RTV/TDF QAM + FAM 20 BID co-ad	A: ATV/RTV/TDF QAM	Ratios of Adjusted Geometric Means Point Estimate (90% CI)
Cmax (ng/mL)	434 (39)	432 (33)	0.940 (0.843, 1.049)*
AUC(TAU) (ng•hr/mL)	4072 (26)	4332 (27)	0.904 (0.838, 0.976)*
Cmin (ng/mL)	78 (22)	86 (30)	0.892 (0.826, 0.963)*
	C: ATV/RTV/TDF QAM + FAM 20 BID temp	A: ATV/RTV/TDF QAM	
Cmax (ng/mL)	446 (40)	432 (33)	0.953 (0.862, 1.054)*
AUC(TAU) (ng•hr/mL)	4141 (23)	4332 (27)	0.919 (0.868, 0.973)*
Cmin (ng/mL)	80 (24)	86 (30)	0.914 (0.849, 0.984)*
	D: ATV/RTV/TDF QAM + FAM 40 QPM	A: ATV/RTV/TDF QAM	
Cmax (ng/mL)	369 (28)	432 (33)	0.906 (0.835, 0.982)*
AUC(TAU) (ng•hr/mL)	3648 (29)	4332 (27)	0.879 (0.845, 0.914)*
Cmin (ng/mL)	72 (33)	86 (30)	0.865 (0.831, 0.899)*
	E: ATV/RTV/TDF QAM + FAM 40 BID temp	A: ATV/RTV/TDF QAM	
Cmax (ng/mL)	367 (32)	432 (33)	0.898 (0.822, 0.982)*
AUC(TAU) (ng•hr/mL)	3486 (32)	4332 (27)	0.834 (0.784, 0.888)
Cmin (ng/mL)	71 (36)	86 (30)	0.834 (0.776, 0.897)

Subjects/Treatment: A: 39, B: 18, C: 18, D: 20, E: 18
co-ad: co-administered, temp: temporally separated (AM FAM dosed 2 h after ATV/RTV/TDF)
* Met the criteria for no-effect: 90% CI within 0.80 - 1.25

- Tenofovir exposures were similar across treatments. Cmax and AUC were within approximately 10% and 17%, respectively, of control values for all treatments

RESULTS

Famotidine:

- Sparse sampling was collected for FAM and no PK parameters were calculated, however concentrations in each regimen were as expected
- FAM 20 mg BID regimens produced maximum concentrations that were approximately 50% of those observed with FAM 40 mg BID dosing, suggesting linear pharmacokinetics

Safety and Tolerability

Table 4. Safety Results

	A: ATV/RTV/TDF QAM N = 40	B: ATV/RTV/TDF QAM + FAM 20 BID (co-ad) N = 19	C: ATV/RTV/TDF QAM + FAM 20 BID (temp) N = 18	D: ATV/RTV/TDF QAM + FAM 40 QPM N =20	E: ATV/RTV/TDF QAM + FAM 40 BID (temp) N = 20
Total # AEs	32	9	5	4	7
# Subjects reporting AEs (%)	21 (53)	3 (16)	5 (28)	3 (15)	5 (25)
Discontinuation due to AEs - n (%)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Most Frequent AEs (≥4 Subjects) - n (%)					
Fatigue	8 (20)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	3 (8)	0 (0)	1 (6)	0 (0)	1 (5)
Diarrhea	1 (3)	0 (0)	1 (6)	0 (0)	2 (10)
Grade 3/4 Lab. Abnormalities - n (%)					
Total Bilirubin[a], Grade 3	26 (65)	6 (32)	4 (22)	3 (15)	4 (20)
Grade 4	6 (15)	0 (0)	0 (0)	1 (5)	0 (0)

[a] Grade 3 Bilirubin: 2.6 - 5.0 x ULN, Grade 4 Bilirubin: >5 x ULN

- There were no reported deaths or serious adverse events in this study. One subject discontinued prior to randomization due to the AE of vomiting
- ATV is a reversible inhibitor of UGT1A1 that is primarily responsible for glucuronidation of bilirubin. Inhibition of UGT1A1 by ATV is associated with benign, reversible hyperbilirubinemia and has not been linked to the development of hepatotoxicity. Elevated bilirubin levels decreased to normal range upon cessation of study drug
- Co-administration of ATV/RTV/TDF and FAM up to 40 mg twice daily was generally safe and well tolerated

CONCLUSIONS

- **When FAM 20 mg twice daily was administered either temporally separated (10 h before and 2 h after) or simultaneously with ATV/RTV and TDF, Cmax and AUC were not affected and an estimated <20% decrease in Cmin was observed**
- **FAM 40 mg administered QPM (12 h prior to ATV/RTV and TDF in the AM) produced similar exposures to both FAM 20 mg BID regimens. Cmax and AUC were minimally affected (~12% reduced). Cmin was 23% lower relative to the control treatment**
- **FAM 40 mg administered twice daily temporally separated from ATV/RTV and TDF (10 h before and 2 h after) resulted in decreases in ATV Cmax, AUC and Cmin of 26%, 21% and 28%, respectively**
- **This study demonstrates several ways to administer ATV/RTV with both TDF and an H_2 receptor antagonist such as FAM**

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